Societal impact of synthetic biology: responsible research and innovation (RRI)

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Abstract

Synthetic biology is an emerging field at the interface between biology and engineering, which has generated many expectations for beneficial biomedical and biotechnological applications. At the same time, however, it has also raised concerns about risks and benefits or about the aim of producing new forms of living organisms. Researchers from different disciplines as well as policy makers and the general public have expressed the need for a form of technology assessment that does not only deal with technical aspects, but also includes societal and ethical issues. A recent and very influential model of technology assessment that tries to implement these aims is known as RRI ("Responsible Research and Innovation"). In this paper we introduce this model and its historical precursor strategies. Based on the societal and ethical issues which are presented in the current literature, we discuss challenges and opportunities of applying the RRI model for the assessment of synthetic biology.

Introduction

Synthetic biology as an emerging field at the interface between biology and engineering has raised many expectations for beneficial and revolutionizing applications, for instance in medicine, for the production of biofuels or for bioremediation. However, there are also concerns that synthetic biology might have negative consequences, such as impacts related to intellectual property rights, potential abuse or unknown side-effects. Moreover, it has been suggested that this new field could raise concerns related to the aim of producing new life forms, which may be perceived as artificial organisms and thus as unnatural. It is important to take potentially negative side-effects of biotechnologies and related concerns of the public seriously. Therefore, different strategies to study risks as well as economic, societal and ethical implications of emerging technologies have been developed. The most recent model runs under the acronym of "RRI", which stands for "Responsible Research and Innovation".

This review will introduce RRI for synthetic biology. In the first part we provide an overview of the societal and ethical implications of synthetic biology which have been examined in the academic literature. We then introduce the model of RRI and its historical precursor strategies. The final part will discuss the challenges and future directions of the RRI model for synthetic biology by reflecting the ethical and societal issues in context of the RRI framework.

1. Different types of concerns on societal and ethical implications of synthetic biology

Synthetic biology is an interdisciplinary field at the interface between biology and engineering, which involves different disciplines such as molecular biology, system biology, biophysics and biotechnology as well as engineering sciences and information technology. It is sometimes described as an extension of earlier forms of genetic engineering. However, the aim is not only to produce new kinds of modified organisms, but also to understand complex biological systems and networks by constructing biological modules and systems that may or may not exist in nature [1,2]. Possible applications of biological systems resulting from synthetic biology could range from energy production through the invention of biomaterials and tools for environmental remediation to various medical applications [3,4]. The latter include so-called theranostic systems, which can sense disease markers and respond by the direct production of therapeutic molecules [5].

The potential of synthetic biology generates hopes and promises. However, at the same time there are also concerns and fears that this technology drifts too far away from nature. The academic literature has discussed different issues and concerns within the current debate [6,7,8,9,10,11]. Many concerns are known from the debate over "Genetically Modified Organisms" (GMO) and have been anticipated to be similar for synthetic biology [12]. However, synthetic biology allows for new dimensions of creativity in biotechnology and novel products that are further away from their natural origins than previous forms of gene technology. Moreover, entirely new types of applications are discussed for this technology, which go along with novel opportunities as well as risks and economic challenges. In the following section, we distinguish between three types of societal and ethical concerns commonly addressed in the academic literature.

1.1. Technical and risk-related concerns

Concerns under this header deal with different risks for human health and the environment. Two different types of concerns are distinguished related to respective risk prevention strategies. Biosafety is the strategy to improve laboratory safety, avoid unintended consequences and deal with the uncontrolled release of synthetic biology products. Biosecurity strategies deal with bioterrorism and the military usage of synthetic organisms.

- *Biosafety:* Pathogens, toxins or otherwise harmful or potentially harmful biological material produced through synthetic biology could be released accidently from a laboratory [1,7,13]. Moreover, unintended side-effects of synthetic biology products created for a certain task (e.g. modified microorganisms used for bioremediation) could occur in the environment and negatively influence human health and other organisms [1,13]. Other risks include the contamination of the natural gene pool through accidental release of synthetic biology products.
- *Biosecurity:* A risk that is widely recognized by the scientific community is that synthetic biology could be misused for the design of pathogens for the purposes of bioterrorism or biological weapons [6,14,15]. Although this dual-use dilemma has been known in life sciences before, the new technical potential of synthetic biology including the possibility of synthesizing the genome of pathogenic viruses or of combining different traits to render microorganism more dangerous have exacerbated the risk of misuse [16].

1.2. Concerns about availability and distribution

Besides these risk-related issues there are concerns that deal with the availability and distribution of synthetic biology and its applications or products. These concerns touch social and economic implications as well as questions of justice and fairness.

- *Patenting and creation of monopolies:* The great expectations of novel products in synthetic biology have triggered a debate over the role of patenting and intellectual property regimes [17]. It has been discussed, for instance, whether patenting of synthetic biology products and processes may lead to the creation of commercial monopolies [17,18]. Moreover, there is a risk that such patents might inhibit innovation in synthetic biology rather than promoting it [9,19,20].
- *Distribution of benefits and risks:* Both, patenting and the potential of monopolies on certain products or applications in the field of synthetic biology, raise concerns that access to the associated knowledge and applications will be unfairly restricted and controlled [11,21]. These concerns – subsumed under the header of justice and fairness – are related to the distribution of benefits and burdens within a society and across the globe. Besides the distribution itself, the question of who should decide how benefits and risks should be distributed has been raised [21,22].

1.3. Concerns about "unnatural life"

The third type of concerns relates to the application of engineering principles and procedures to living organisms in order to design new forms of life. In context of the famous synthetic biology competition iGEM ("The international Genetically Engineered Machine Competition"), scientists even speak of genetically engineered *'machines'*.

- *Creating artificial life:* The engineering-driven approach of understanding living organisms raised moral concerns about the possibility that artificial life might be created and that this could amount to interference with nature [10,23,24]. Some ethicists argue that living organisms have a moral status, meaning that they should be treated differently from mere things: for such positions, synthetic biology raises the question of whether this status may be affected by the artificial nature of these organisms [25,26,27]. Speaking of a moral status in living organisms evokes the fear that researchers in synthetic biology are 'playing God' or – in a more secular sense –are 'tampering with nature'. The question 'What is life?' can be interpreted differently – referring to a variety of philosophical, religious or scientific concepts [24,28,29]. Certain views on life go along with the idea that life should be 'natural'. This raises concerns about the unnatural aspect of synthetic biology products [30,31]. Another common moral concern claims that synthetic biology has a reductionist approach and erodes the distinction between organisms and machines [20].

2. Responsible research and innovation in the field of synthetic biology – challenges and prospects

Not only academics in the literature but also the lay public have expressed issues and concerns as those mentioned above [31,32,33]. Since it is the scientific work that has caused these concerns, it has been suggested that scientists should interact with the public and discuss its societal and ethical concerns. Various approaches towards the assessment and governance of emerging technologies – such as synthetic biology – have been developed. Recent approaches put a particular emphasis on considering societal and ethical concerns of the public. It has been suggested that scientists could assume their responsibility towards society in participatory approaches. In such approaches scientists interact with the public in the form of stakeholders or selected representatives to assess the technology in question. Particularly in Europe, the currently most influential model of assessing, evaluating and accompanying emerging technologies together with the public is known as "Responsible Research and Innovation" (RRI). In the following section, we introduce the model of RRI and compare it to its historical precursors. Subsequently, we will give a short overview of the current debate over the application of the RRI model in synthetic biology.

2.1. RRI and its historical precursors

The idea that the development of technologies goes along with responsibilities of scientists and engineers towards society is not new. Historical precursors or related concepts of RRI are different versions of "technology assessment" (TA) and so-called ELSI/ELSA programs[1], where the acronym stands for "ethical, legal and social implications" or "aspects". Although these different models all deal with the impact of science and research on society and the environment, the focus of what constitutes responsible research has slightly shifted with the transition from one model to the other.

Technology assessment (TA) is one of the main roots of RRI. It was the leading approach of evaluating and regulating new technologies from the 1970s to the 1990s [34]. The aim of the traditional TA approach was to evaluate new technologies in order to give early warnings and avoid or compensate anticipated negative impacts. Originally, this model was more focused on a technical evaluation than on the discussion of ethical issues. In the mid-1980s Arie Rip and colleagues have refined this model by considering feedbacks from users and the society for the design and construction of new technologies [35]. This revised version of TA was called "constructive technology assessment" (cTA) [35]. Another TA-model called "participatory technology assessment" (pTA) does not set as much emphasis on the design of the assessed technology as cTA. Instead, it evaluates the impact that a technology has for society by involving public actors [36]. Such representatives from the public include citizens, consumers and interest groups; they are part of the process of assessing and debating socially sensitive scientific and technological issues [37].

[1] While the acronym "ELSA" is commonly used in Europe, "ELSI" is more prevalent in the USA.

The *ELSA/ELSI model* became well-known in the 2000s and had their 'golden years' between 2002 and 2012 [38]. The first example of such a program dates back to 1988 when James Watson as director of the "Human Genome Project" (HGP) declared at a press conference that the ethical and social implications of genomics warrant a special effort and should be directly funded as part of the HGP by the U.S. National Institutes of Health (NIH) [39]. The first program funded by the NIH was then launched in 1990. Since 2000 ELSA/ELSI became rather popular and programs were initiated in Canada, South Korea and Europe. Typically, the ELSA/ELSI model is embedded in large-scale scientific programs and addresses the interaction between internal technological and external social processes that could shape technological evolution. In contrast to the classical TA-approaches, these programs explicitly address ethical and legal aspects. As a consequence, the ELSA/ELSI model focuses on interdisciplinary collaborations as well as interactions with different stakeholders from society.

The *RRI model* is a recent science governance approach which emerged around the 2010s and has been included in the "European Framework Programmes". The RRI model takes up many elements of ELSA/ELSI; therefore, it has been argued that the differences between ELSA/ELSI and RRI tend to be exaggerated [38]. RRI considers societal needs and concerns through an interactive process in which societal stakeholders and innovators respond to each other [40,41,42]. The RRI model suggests that responsible developments in science, technology and industry should be combined in the way that responsible innovations are anticipatory, reflective, deliberative and responsive [43]. The inclusion of ethical acceptability and societal desirability in the process of innovation is considered to be helpful to better embed scientific and technological advances in society [41]. Thus it has been suggested that ethical reflection and anticipation should be included in the research agenda of the assessment of emerging technologies. The involvement of these topics should help to analyze and interpret technological applications and their presumable future impact on society and the environment. In comparison to ELIS/ELSA, the RRI approach is more focused on socio-economic benefits and collaboration with private and industrial partners [38]. Moreover, RRI should accompany the research process rather than evaluating its consequences [44,45]. For this purpose, the research community and the education community should be brought together with representatives from industry and business as well as from the general public and policy makers [46]. According to the European Union [46], RRI is not only characterized by public engagement and the inclusion of ethical issues, but also by aspects such as science education and open access to knowledge.

In the contemporary literature on the RRI model, different strategies to make RRI operative and effective have been discussed [40,41,42,47]. For instance, establishing a responsible research includes addressing societal needs and challenges in defining the purpose of science [42]. According to the RRI model, bearing responsibility would mean that scientists interact with the public in a democratic deliberative approach. Democratic deliberation can be understood as an active participation of citizens and a form of collaborative decision-making that embraces a respectful debate of opposing views [9]. The inclusion of the public can happen in the form of consensus conferences, citizens' juries, deliberative mapping, deliberative polling or focus groups [40].

2.2. Establishing RRI in the field of synthetic biology

The reflection on the societal and ethical implications of synthetic biology began at an early stage – almost in parallel to the emergence of this novel field. Based on the experience with the debate over green gene technology, the scientific community wanted to avoid making the same mistakes of introducing a new technology before its ethical and societal implications were discussed. Shortly after the first viral and bacterial genomes were produced synthetically at the beginning of the new millennium, first publications – authored, among others, by scientists – discussed synthetic biology from the perspective of "technology assessment"

[6,14,16,48,49]. Issues that were discussed in these publications included the previously introduced concerns on bioterrorism, biosecurity, laboratory safety, environmental protection, intellectual property rights and general ethical concerns.

Since the emergence of synthetic biology, different initiatives and programs were launched worldwide to anticipate and discuss its societal and ethical implications. Examples include the U.S. programs "Synthetic Biology Engineering Research Center" (SynBERC), running since 2006, and "Synthetic Biology Project" (www.synbioproject.org), starting in 2008, the European project "Making Perfect Life", which was launched in 2009 by the Science and Technology Options Assessment (STOA) panel of the European Parliament, or the national projects "Engineering Life" and "SynbioTA", both launched in 2010 by the Federal Ministry of Education and Research in Germany. Other national and transnational activities were, for instance, the programs "SYNBIOSAFE" (2007-2008), "SYBHEL" (2008-2012), "Synthetics" (2009-2011), "GEST" (2011-2014), "SynGovernance" (2012-2014) and "Synenergene" (2013-2016). All of these initiatives and programs included or focused on the ethical and societal implications of synthetic biology and referred to the ELSI/ELSA or the RRI model. Despite differences in their scopes and aims, there is a broad consensus among scientist within these programs that public engagement is essential for the development of regulatory regimes [50,51,52].

3. Challenges and future directions of RRI for synthetic biology

So far the debate over synthetic biology and its societal and ethical implications have produced an impressive number of reports and academic publications. However, these documents are usually based on anticipated implications and anticipated risks and benefits of synthetic biology as there have not been any applications on the market yet [53]. Therefore, societal and ethical implications have usually been considered in comparison with similar applications from other biotechnologies (e.g. green gene technology) or by analyzing the worldviews conveyed by the aims of synthetic biology that speak of engineered living organisms and synthetic cells [29]. This speculating nature is one of the main challenges for RRI programs on synthetic biology.

As introduced above, RRI is usually implemented in the form of a participatory approach, meaning that scientists interact with the public by, for instance, establishing a dialogue to scrutinize ways in which emerging science is imagined, to explore possible future ways including societal and ethical issues or to define the direction of innovations [54]. Moreover, the research agenda of the RRI model includes the point of view of ethics and social sciences. In the following paragraphs we will address the challenges of implementing such an RRI model for synthetic biology.

3.1. Challenges for applying RRI to synthetic biology

One of the main challenges for applying the RRI model to synthetic biology is dealing with responsibility under the conditions of the high degree of uncertainty of the future directions of this novel field: compared to established technologies such as green gene technology there is almost no valid prospective knowledge available [53]. If the aim of anticipating and reflecting the impact of synthetic biology and the idea of a participatory approach of RRI are taken seriously, responsibility will not be demanded from scientists alone. It is a question of the distribution of responsibility [47]: stakeholder groups, the lay public as well as policy makers have to bear responsibility, too. Thus, as Cecilie Glerup and Maja Horst put it, responsibility is something that different actors learn together in a deliberative process [55]. In that sense, the RRI model – applied to synthetic biology – should be a task carried out by the whole society and not only by the scientific community.

Another important challenge for applying RRI to synthetic biology is the great variety of possible products, applications and potential uses. Amy Wolfe, for instance, suggests establishing goals that do not just cover the type of production, but also determine how research findings are used [56]. According to Wolfe, this kind of specificity in assessing and defining goals could support the research on societal aspects of synthetic biology as well as the process of public engagement [56]. Consequently, it may not be sufficient to define scientific and technical goals; in addition, a research agenda on societal and ethical perspectives has to be established. This would mean that – in parallel to the development of scientific and technical goals – there is a need for a strategy on how to integrate societal and ethical perspectives into the research agenda [57]. However, that seems to be a huge challenge due to the different kind of societal and ethical concerns raised by synthetic biology. Moreover, the integration of societal perspectives should influence innovation without preventing scientific curiosity and engineering creativity.

The idea of giving a strong weight to the inclusion of the public in the RRI process goes along with several other challenges. One of them directly relates to the issues and concerns introduced in the first section: the public should certainly be involved because certain concerns only come to the light in direct consultation of laypersons. However, the identification of other issues requires the insight of experts and is not evident to the public. Moreover, experts are necessary for the analysis and interpretation of concerns, including those that have originally been raised by the public. This analysis should generate arguments that help to evaluate how these issues could influence the further development of synthetic biology. For such an analysis, different types of expertise and collaborations between scientists, engineers and researchers in social sciences and humanities are crucial [58]. In the following, we list some examples for points that should be considered in such an interdisciplinary collaboration:

- *Technical and risk-related concerns* should be investigated with well-established technology-assessment tools that examine how synthetic biology products react, for instance, to different environmental conditions.

- *Concerns about the availability and distribution* of synthetic biology products should be analyzed and interpreted by experts from ethics and law as well as from social science and economics.
- Experts from ethics and law, supported by those from social science and other disciplines, should scrutinized ethical *concerns about creating artificial life*.

In consequence, it seems to be important that besides the inclusion of the public, the RRI framework should leave enough space for experts to examine the different societal and ethical issues, develop strategies on how to deal with them and how to communicate them. It is crucial that experts from science and other disciplines should communicate their analysis and interpretation in an open and transparent way to the laypersons in a public education as well as engagement process [29].

3.2. Future directions of the assessment of synthetic biology

The discussion of societal and ethical implications of synthetic biology started at a very early stage. Therefore, a debate was established long before any concrete products had been developed. The discussion of societal and ethical issues is based, for instance, on an anticipation of new possibilities associated with synthetic biology as well as an analysis of the worldviews and aims conveyed by that technology, including the human relation to nature. Perhaps the early debate over the impacts of synthetic biology as well as the novel assessment approach of RRI might help to avoid conflicts as they are known from, for instance, green gene technology. However, it is still possible that the availability and commercialization of specific synthetic biology products might create novel conflicts. Helge Torgersen and Markus Schmidt argue that conflicts might be unavoidable and could be the best stimulus for an open and transparent debate [59]. This could mean that the aim of the RRI model to promote interactions between scientists, experts from other fields and the public might be a suitable framework to deal with certain conflicts in a constructive way.

The RRI model emphasizes that the focus on assessing an emerging technology like synthetic biology should not be focused on concerns about risks and negative consequences of a technology alone. Instead, technology assessment should also be included in the process of innovation and invention. One of the huge challenges certainly is to include the public in this process and to collectively analyze societal and ethical concerns amongst natural *and* social scientists. The implementation of the RRI model for synthetic biology has to manage the balancing act between shaping research and innovation through public participation and leaving enough space for scientific curiosity and engineering creativity.

Summary

- Synthetic biology as an emerging field at the interface between biology and engineering has raised concerns about risks, distribution and about the aim of producing new forms of living organisms.
- RRI (Responsible Research and Innovation) is the most recent model to deal with risk and societal or ethical concerns. Well-known RRI precursors are: technology assessment (TA) and ELIS/ELSA (ethical, legal and social implications/aspects).
- In comparison to the precursors, RRI sets a particularly strong focus on addressing ethical and societal issues already in the phase of innovation which should allow to include societal needs and priorities in shaping technological applications. For this purpose RRI emphasizes the importance of involving lay people in participatory processes.
- Challenges for applying the RRI model to synthetic biology include 1) the uncertainty with respect to the possibilities in this techno-science, 2) finding apt models of involving the public, and 3) influencing the innovation process without hindering scientific curiosity and engineering creativity.

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Conflict of interests

The authors declare that they have no conflict of interest.

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